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High Rate of Fatal Cases of Pediatric Septicemia Caused by Gram-Negative Bacteria with Extended-Spectrum Beta-Lactamases in Dar es Salaam, Tanzania

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Extended-spectrum beta-lactamases (ESBLs) were present in high proportions of *Escherichia coli* (25% [9 of 36]) and *Klebsiella pneumoniae* isolates (17% [9 of 52]) causing pediatric septicemia at a tertiary hospital in Tanzania. Patients with septicemia due to ESBL-producing organisms had a significantly higher fatality rate than those with non-ESBL isolates (71% versus 39%, $P = 0.039$). This is the first report of the CTX-M-15 genotype of ESBLs on the African continent and the first observation of SHV-12 genotype in an isolate of *Salmonella enterica* serotype Newport.

Resistance to beta-lactam antibiotics was demonstrated in *Escherichia coli* even before penicillin was released for clinical use. In the 1960s, the first plasmid-transferable beta-lactamase was discovered and named TEM-1 after Temoniera, the Greek girl who harbored the *E. coli* isolate from which the enzyme was obtained. Since the 1980s, a large number of plasmid-transferable extended-spectrum beta-lactamases (ESBLs) capable of inactivating extended-spectrum cephalosporins has been discovered (6). Most of the ESBLs are derived from TEM-1 and SHV-1 (sulfhydryl variable) by mutations. ESBLs have spread widely and have become a major cause of nosocomial infections associated with high mortality rates, particularly in serious infections such as septicemia (12). In Africa, ESBLs have been reported in Egypt (19), Tunisia (4, 5), Morocco (2), Senegal (18, 20), Nigeria (1), South Africa (9), and Kenya (11) but not previously from Tanzania. In the present study, we investigated the prevalence and clinical implications of ESBL production in *E. coli*, *Klebsiella pneumoniae*, and salmonellae causing septicemia in infants and children admitted to a tertiary teaching hospital in Tanzania.

MATERIALS AND METHODS

From August 2001 to August 2002, blood cultures were obtained from 1,798 children aged 0 to 7 years with a fever of ≥38°C or other signs of severe infections admitted to the Pediatric Department at Muhimbili National Hospital, a tertiary referral hospital in Dar es Salaam, Tanzania. We included in the present study 113 children who had growth in blood culture of one or more isolates of *E. coli*, *Klebsiella* spp., or salmonellae.

Blood specimens (1 ml from neonates and 5 ml from older children) were inoculated in BACTEC Myco/F lytic blood culturing vials (Becton Dickinson, Franklin Lakes, N.J). Positive blood cultures were subcultured on Columbia II agar base (Oxoid Ltd, Basingstoke, United Kingdom) with 5% human blood, chocolate agar, and MacConkey agar (Difco/BD Diagnostic Systems, Sparks, Mich.). The isolates were identified according to established procedures (7). *Klebsiella* spp. were identified with the API 20E system (bioMérieux SA, Marcy l'Etoile, France). Susceptibilities against antimicrobial agents were tested by the disk diffusion method according to NCCLS guidelines (15). Isolates of *E. coli*, *Klebsiella* spp., and salmonellae with reduced susceptibilities to cefotaxime (zone diameter of ≤27 mm) and/or ceftazidime (zone diameter of ≤22 mm) according to guidelines for laboratory detection of ESBLs from the Centers for Disease Control and Prevention (http://www.cdc.gov/ncidod/hip/Lab/FactSheet/esbl.htm) were tested for ESBL phenotype with three different Etest ESBL strips, ceftazidime–ceftazidime+clavulanate, cefotaxime–cefotaxime+clavulanate, and cefepime–cefepime+clavulanate (AB Biodisk, Solna, Sweden). Isolates were reported as having ESBL phenotype if one or more of the three ESBL Etests were positive. In accordance with instructions from the manufacturer (AB Biodisk), the ESBL Etest was considered positive if the ratio between the MICs of the cephalosporin and the cephalosporin-clavulanate combination was ≥8 or if the test showed a characteristic rounded "phantom" inhibition zone or a deformed inhibition zone surrounding the part with cephalosporin without clavulanate. Isolates with the ESBL phenotype were examined for the presence of bla_{TEM}, bla_{SHV}, and $bla_{CTX\text{-}M}$ by PCR (11, 16, 17).

After purification with a QIAquick PCR purification kit (Qiagen, Hilden, Germany), the PCR products were sequenced with the ABI Prism BigDye cycle sequencing ready reaction kit (PE Biosystems, Norwalk, Conn.) by using the same primers. The products were analyzed on an ABI Prism 3700 DNA sequencer (PE Biosystems). Sequences were aligned with known ESBL sequences (www.lahey.org/studies/) by using Vector NTI version 6 (Informax, Frederick, Md.). Amplified fragment length polymorphism (AFLP) analysis was performed as previously described (22) with minor modifications. The Pearson coefficient of similarity of AFLP curves was calculated, and cluster analysis was performed by unweighted paired group method with arithmetic averages (UPGMA) by using BioNumerics version 3.0 (Applied Maths, Kortrijk, Belgium). Two isolates were considered to be identical if the similarity was ≥95% (22).

RESULTS

A total of 48 isolates of *K. pneumoniae* and 4 additional isolates of *Klebsiella* spp. were recovered from 48 patients. A total of 36 *E. coli* isolates were recovered from 33 patients, and 37 isolates of various *Salmonella enterica* serotypes (two serovar Typhi, 15 serovar Typhimurium, 19 serovar Enteritidis, and 1 serovar Newport) were isolated from 37 patients. Fifteen patients had polymicrobial infections, of whom eight patients had mixed infections with pathogenic bacteria other than

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TABLE 1. Distribution of ESBL genotypes in bacteria isolated from children with septicemia at a tertiary hospital in Tanzania

Isolate	No. of cases (%)[a] positive for:			Total no. (%)
	E. coli	*Klebsiella* spp.	Salmonellae	
ESBL isolates	9 (25)	9 (17)	1 (3)	19 (15)
TEM-63	4	3	0	7
SHV-2a	0	2*	0	2*
SHV-12	0	2	1	3
CTX-M-15	5	1*	0	6*
ESBL, other cause	0	2	0	2
Non-ESBL isolates	27 (75)	43 (83)	36 (97)	106 (85)
Total isolates in study	36 (100)	52 (100)	37 (100)	125 (100)

[a] *, One isolate of *K. pneumoniae* had both the SHV-2a and the CTX-M-15 genotypes.

E. coli, *Klebsiella* spp., and salmonellae and three patients had concomitant candidemia.

A total of 19 isolates with ESBL phenotype were recovered from 16 patients. The proportions of isolates with ESBL phenotypes and genotypes are shown in the Table 1. Table 2 shows the number of patients with septicemia caused by bacterial isolates with different ESBL types and the clinical outcomes for these patients. Among all salmonella isolates, only one isolate (serovar Newport) had ESBL. Sequencing data yielded conclusive evidence for an ESBL genotype for all isolates with ESBL phenotype except for two isolates of *K. pneumoniae*. Furthermore, several isolates had TEM-1 and SHV-1 genotypes, which are not ESBL genotypes (Fig. 1).

The ESBL-producing isolates showed higher rates of resistance toward most of the commonly used drugs at the hospital, and the difference was particularly striking for gentamicin and chloramphenicol. All ESBL-producing isolates were susceptible to meropenem, and all but one *E. coli* isolate were susceptible to ciprofloxacin. All isolates containing TEM-63, SHV-2a, or SHV-12 were resistant to gentamicin, chloramphenicol, doxycycline, and trimethoprim-sulfamethoxazole. For all CTX-M-15 isolates the cefotaxime MICs were >16, whereas for all TEM-63 isolates the cefotaxime MICs were <2 (Fig. 1).

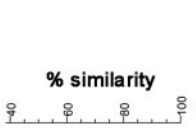
We evaluated the clinical characteristics of patients with septicemia caused by *E. coli*, *Klebsiella* spp., and salmonellae. A longer time from admission to blood culture was the only statistically significant ($P = 0.003$) risk factor for septicemia with ESBL-producing organism as determined by univariate analysis, and this risk factor remained significant in a logistic regression model that included the variables age (dichotomized for neonates ≤1 month and for older children) and polymicrobial infection.

Treatment outcome, dichotomized as dead or alive on discharge, could be verified for 99 of the 113 study subjects, among whom 43 died while in the hospital. Patients with septicemia due to ESBL-producing organisms had a significantly higher fatality rate than those with non-ESBL isolates (71% versus 39%, $P = 0.039$). Inappropriate chemotherapy per se was also significantly ($P = 0.002$) associated with fatal outcome, and this association was borderline significant ($P = 0.060$) also when only inappropriate treatment due to other causes of resistance than ESBL was considered. Both ESBL phenotype and inappropriate chemotherapy due to other mechanisms were independent significant risk factors for fatal outcome in a logistic regression model, which included age (dichotomized) and polymicrobial infections. Figure 2 shows Kaplan-Meier survival estimates from the day of admission for patients with septicemia caused by ESBL-producing and non-ESBL-producing isolates. Although the mortality associated with non-ESBL-producing isolates is greatest during the first few days, the mortality associated with septicemia due to ESBL-producing organisms peaked more than a week after admission. Figure 3 shows that the mortality associated with septicemia caused by ESBL-producing isolates appears to lag several days behind that in patients who received "inappropriate chemotherapy" due to resistance caused by mechanisms other than ESBL.

TABLE 2. Characteristics of 16 children with septicemia caused by ESBL-producing bacteria

Patient	Sex	Age	Ward	Isolate no.	Organism	ESBL genotype	Outcome
1	F	6 mo	17	32	*E. coli*	TEM-63	Death
2	M	3 yr	Mak	77	*E. coli*	TEM-63	Death
3	F		B2	112	*E. coli*	TEM-63	Death
				113	*E. coli*	TEM-63	
4			36	85	*E. coli*	CTX-M-15	
5	M	0 day	36	81	*E. coli*	CTX-M-15	Death
6	M	7 mo	B1	69	*E. coli*	CTX-M-15	Recovery
7	F		Mak	114	*E. coli*	CTX-M-15[a]	
				115	*E. coli*	CTX-M-15[a]	
				107	*K. pneumoniae*	Unknown[b]	
8	M		Mak	104	*K. pneumoniae*	TEM-63	Death
9	F	1 yr	Mak	102	*K. pneumoniae*	TEM-63	Death
10	M	2 yr	17	103	*K. pneumoniae*	TEM-63	Recovery
11	M	4 yr	B2	101	*K. pneumoniae*	SHV-12	Death
12	M	11 mo	Mak	109	*K. pneumoniae*	SHV-12	Recovery
13	M	1 yr	17	105	*K. pneumoniae*	SHV-2a	Death
14	F	1 day	36	91	*K. pneumoniae*	SHV-2a, CTX-M-15	Recovery
15		8 day	36	110	*K. pneumoniae*	Unknown[c]	Death
16	M		A2	66	*S. enterica* serovar Newport	SHV-12	Death

[a] The patient had two CTX-M-15-producing *E. coli* isolates with unrelated AFLP patterns.
[b] The isolate had a SHV-1 genotype.
[c] The isolate had a TEM-1 and SHV-1 genotype.



ID	Species	Ward	TEM	SHV	CTX-M	Cefotaxime MIC	Cefotaxime clavulanate MIC	Ceftazidime MIC	Ceftazidime clavulantate MIC	Cefepime MIC	Cefepime clavulanate MIC
control	E. coli (Norway)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
113	E. coli	b2	63	-	-	0.5	0.032	>32	0.125	1.5	<0.064
32	E. coli	17	63	-	-	1.5	0.032	>32	0.25	8	<0.064
115	E. coli	mk	1	-	15	>16	0.064	24	0.125	>16	<0.064
114	E. coli	mk	1	-	15	>16	0.064	>32	0.125	>16	0.064
77	E. coli	mk	63	-	-	1	0.125	>32	0.38	1.5	<0.064
112	E. coli	b2	63	-	-	0.5	0.032	>32	0.19	1.5	<0.064
69	E. coli	b1	1	-	15	>16	0.064	>32	0.25	>16	<0.064
81	E. coli	36	1	-	15	>16	0.25	>32	0.19	>16	0.125
85	E. coli	36	1	-	15	>16	0.032	16	<0.064	>16	<0.064
66	S. Newport	a2	1	12	-	>16	0.064	>32	0.19	>16	<0.064
102	K. pneumoniae	mk	63	1	-	0.5	0.032	>32	0.19	2	<0.064
103	K. pneumoniae	17	63	1	-	0.75	0.032	>32	0.19	2	<0.064
104	K. pneumoniae	mk	63	1	-	0.75	0.032	>32	0.25	1.5	<0.064
101	K. pneumoniae	b2	1	12	-	3	0.032	>32	0.125	0.5	<0.064
109	K. pneumoniae	mk	-	12	-	1.5	0.047	>32	0.19	0.38	<0.064
91	K. pneumoniae	36	1	2a	15	>16	0.064	>32	0.19	>16	<0.064
110	K. pneumoniae	36	1	1	-	2	0.032	16	0.094	0.38	<0.064
105	K. pneumoniae	17	-	2a	-	3	0.032	>32	0.094	0.38	<0.064
107	K. pneumoniae	mk	-	1	-	3	0.032	>32	0.094	0.38	<0.064

FIG. 1. AFLP dendrogram of ESBL-producing bacterial isolates as evaluated by Pearson and UPGMA analysis. The diagram also shows the TEM, SHV, and CTX-M genotypes of the isolates and the MICs of ceftazidime, cefotaxime, and cefepime with or without clavulanate by using the ESBL Etest. -, Not detected; ND, no data.

AFLP analysis indicated that three isolates of *K. pneumoniae* with TEM-63 ESBL genotype were identical (Fig. 1). These three isolates were obtained from three different patients from two different wards. None of the other ESBL-producing strains appeared to be related as assessed from the AFLP patterns.

ESBL genotypes were found in all five pediatric wards. There was no obvious confinement of particular genotypes to specific wards. Only CTX-M-15 and SHV-2a genotypes were found in the neonatal ward (ward 36). All of the isolates containing TEM-63 were obtained between the end of December 2001 and early April 2002. Two genetically related TEM-63-containing *K. pneumoniae* isolates were obtained from the same ward with 2.5 months difference in time. The CTX-M-15-containing isolates were obtained throughout the study period.

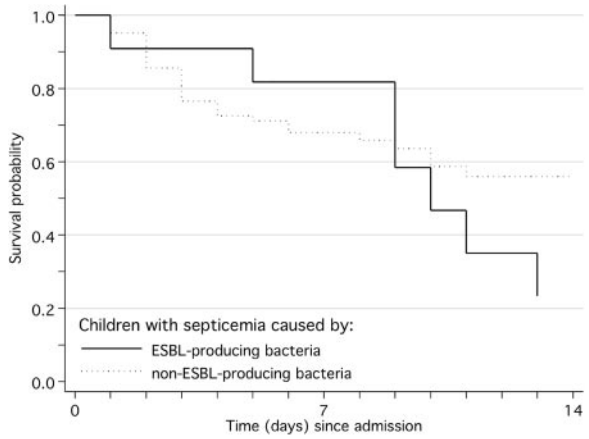


FIG. 2. Survival time (in days) after admission to the hospital of children with septicemia caused by *E. coli*, *Klebsiella* spp., or salmonellae with or without ESBL. Lines: solid, children with septicemia caused by ESBL-producing bacteria; dashed, children with septicemia caused by non-ESBL-producing bacteria.

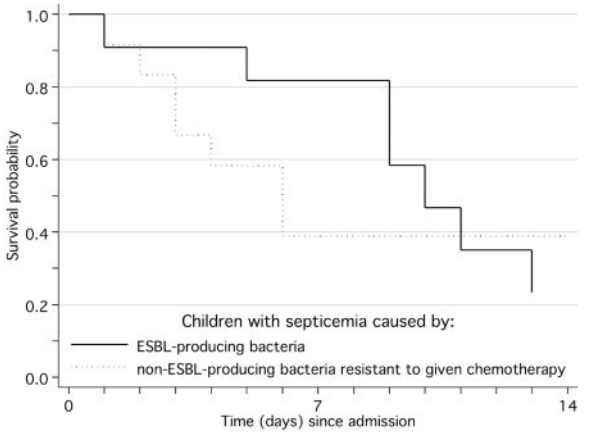


FIG. 3. Survival time (in days) after admission to the hospital of children with septicemia caused by *E. coli*, *Klebsiella* spp., or salmonellae with or without ESBL. Lines: solid, children with septicemia caused by ESBL-producing bacteria; dashed, children with septicemia caused by bacteria that did not have an ESBL phenotype but were resistant to the given antimicrobial chemotherapy due to other mechanisms.

DISCUSSION

This is the first report of TEM, SHV, and CTX-M type ESBL-producing bacteria in Tanzania and one of few reports on ESBLs from Sub-Saharan Africa (1, 9, 11, 18, 20, 21). The proportions of ESBL-producing *E. coli* (25%) and *Klebsiella* spp. (17%) in the present study are higher than those reported from South Africa and comparable to ESBL-affected institutions in US, Taiwan, mainland China, and Japan (6).

CTX-M-15 has been found in India, Japan, Europe, and elsewhere (13); however, this is the first report of the CTX-M-15 genotype on the African continent. CTX-M-12 has previously been reported in *K. pneumoniae* isolates from Kenya (11).

The SHV-12 type ESBL was first discovered in Switzerland and has since been reported from many parts of the world. This is the first time SHV-12 type ESBL has been reported from an isolate of *Salmonella* serovar Newport. Recently, SHV-12-like ESBL was reported in isolates of the *Salmonella* serovars Enteritidis and Babelsberg obtained in France from several children adopted from a particular orphanage in Mali (21). However, apart from this, our study is the first account of SHV-12 genotype ESBL from Sub-Saharan Africa.

TEM-63 has previously been found in South Africa (9), and the finding of this genotype in Tanzania here implies that resistance conferred by this genotype could be a regional problem.

We demonstrate that septicemia caused by these organisms is associated with very high fatality rates. Multivariate analysis identified ESBL phenotype, as well as inappropriate treatment due to other causes of resistance, as independent risk factors for fatal outcome.

Genotyping with AFLP indicated the probable nosocomial spread of one of the ESBL-producing *K. pneumoniae* strains with TEM-63 genotype. Kaplan-Meier survival graphs indicate that the majority of deaths in patients with septicemia due to ESBL-producing bacteria occurred approximately 1 week after admission, whereas the mortality associated with non-ESBL-producing isolates was greater during the first few days after admission. The time from admission to blood culture was the only significant risk factor for infection with ESBL. The clinical findings indicate that the ESBL resistance traits are spreading nosocomially. However, one would expect more homogeneity in AFLP patterns of common genotypes if nosocomial spread was the predominant route of transmission. It is possible that the spread of ESBL traits at the hospital involve transfer of extrachromosomal elements, which would not necessarily be detected by the AFLP method. ESBL genes of the TEM, SHV, and CTX-M families can reside in conjugative plasmids (3, 6, 10, 11, 16), and this has recently been demonstrated for CTX-M-15 (8, 13). Previous reports have demonstrated that ESBL genes can spread not only by epidemic strains but also by plasmid dissemination between unrelated strains (5). One study found the same ESBL gene (TEM-24) in as many as four different species of *Enterobacteriaceae* in a single patient (14). The presence of identical ESBL genotypes in multiple bacterial species in the present study seems to support the notion that interspecies plasmid dissemination may contribute to the spread of ESBLs in our setting also.

The spread of ESBLs on the African continent has grave implications for already strained health care systems. Although treatment of infections with ESBL-producing bacteria remains difficult in high-income countries, the challenge is formidable in the setting of a low-income country where expensive second-line antimicrobial drugs are unavailable and microbiological diagnostic testing is accessible only in a few referral hospitals. Simple hygienic measures, such as hand-washing practices, the use of sterile equipment (particularly for intravenous access and when possible), and patient cohorting (i.e., grouping patients with similar infections in the same location) can help prevent the further spread of these resistance traits. The study underscores that antimicrobial resistance is a global problem and emphasizes the need for surveillance and promotion of correct and restrictive antibiotic policies to halt the further spread of these multiresistant bacteria.

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